REMARKS

With entry of this amendment, claims 1-16, 18, 22-37 and 39-61 are pending. Claims 17, 19-21 and 38 are cancelled. Claims 1, 3- 4, 9, 13-15, 22, 24-25, 30, 35, 41-44, 49, 51 and 53-58 are amended as shown in the claim listing on pages 4-16. Claims 60-68 are newly added. Support for these newly-added claims is found at [0045].

This amendment is consistent with the Restriction Requirement issued October 7, 2004, and cancels subject matter not elected by Applicant in response to said Requirement. Moreover, this amendment also corrects spelling errors and makes the pending claims consistent with the claims pending in parent case 09/853,731.

These amendments made herein to the claims are fully supported by the specification and are not believed to introduce any new subject matter.

Reconsideration of this application, as amended, is respectfully requested.

Informalities

Figure 10, page 5 of the drawings is objected to inasmuch as the label is on a different page from the Figure. This inadvertent error has been corrected and applicant submits herewith a substitute page 5 of the Figures.

Claim Objections

Claims 14, 17, 35 and 38 are objected to for containing non-elected subject matter. Claims 14 and 35 are amended to delete non-elected sequence modifications. Claims 17 and 38 are cancelled.

Claims 53, 55 and 57 are objected to because of the use of the "$^{\pm}$" symbol. These claims are amended to now show "±" as suggested by the Examiner.

Obviousness-Type Double Patenting Rejections

Claims 1, 18, 22, 39 and 49-58 are provisionally rejected under the doctrine of obviousness-type double patenting as not being patentable over claims 1-16 of co-pending Application No. 10/104,363 (CD 20805). Inasmuch as there are no allowed claims in either application, applicant requests that this provisional rejection be held in abeyance until there is an indication of allowable subject matter in either application at which time the applicant can then assess whether there is any overlap in the allowed claims.

Alternatively, applicants respectfully submit that this rejection is not proper. The claims of the instant application are directed to a specific pharmaceutical formulation containing an erythropoietin glycoprotein while the claims of co-pending Application No. 10/104,363 (CD 20805) are directed to a particular erythropoietin glycoprotein product, in whatever form, not just in a pharmaceutical formulation. These different types of claims, compound versus formulation claims, are not properly subject to an obviousness double patenting rejection.

Claims 1-59 are also provisionally rejected under the doctrine of obviousness-type double patenting as not being patentable over claims 1-11, 13-17, 19, 23-36, 38-42, 48-55, 59-61, 67-77 and 83-89 of co-pending Application No. 09/853,731 (CD 20619 US). Similarly to the immediately previous rejection, inasmuch as there are no allowed claims

in either application, applicant requests that this provisional rejection be held in abeyance until there is an indication of allowable subject matter in either application at which time the applicant can then assess whether there is any overlap in the allowed claims.

The Section 112 Rejections

Claims 4, 9, 25, 30 and 58 are rejected under 35 USC § 112, second paragraph, as being indefinite. This rejection is overcome.

Specifically, claims 4 and 25 are alleged to be indefinite for stating that citrate is a multiple charged inorganic anion. Claims 4 and 25 are amended to delete reference to citrate.

Claims 9 and 30 are alleged to be indefinite in their use of the term "arginine/H_2SO_4/Na_2SO_4" as being a buffer to retain a pH of 5.5-7.0. Claims 9 and 30 are herein amended to delete reference to arginine/H_2SO_4/Na_2SO_4.

The term "poloxamers type 188 in an amount of 0.1 mg" in claim 58 is alleged to be indefinite as the volume of solution is not indicated. Claim 58 is amended to indicate that, consistent with the other units of measurement given in the claim, the poloxamers are present in an amount of 0.1 mg/mL.

The Section 102 Rejections

Before specifically addressing the art rejections, it is noted that independent claims 1, 22 and 49 are amended to include methionine. The use of methionine as a preferred

antioxidant is supported in the specification, *inter alia*, at [0044]. Claims 1 and 22 as now amended also specify that the claimed liquid compositions are stable at room temperature for at least about six months. This amendment is supported by the specification, *inter alia*, at [0005] and Table 3.

Claims 1-4, 6-9 and 11 are rejected under Section 102(b) as being anticipated by EP 0909564 (Yamazaki). This rejection is overcome.

Unlike the current application, Yamazaki does not recognize, much less address, the problem of protein aggregation/oxidation when the erythropoietin glycoprotein product-containing composition is left at room temperature. Applicant specifically recognized (application at [0005]) and addressed this problem by the inclusion of an antioxidant (*see, e.g.* [0044] and Figure 8). At paragraph [0005] of the instant application applicant specifically indicates that stable at room temperature in the context of the invention means reduced degradation "(e.g. aggregation or denaturation) and chemical changes (e.g. oxidation or modification of chemical bonds in general) of the protein...." That Yamazaki did not recognize the problem of protein aggregation/oxidation is evidenced by his assessment of stability of the protein by use of reverse phase HPLC (rpHPLC) alone. While this method allows for assessment of total protein, it does not discriminate between native protein and aggregated and/or oxidized protein. This is a significant distinction as not all protein that is recovered by rpHPLC is actually in the native state. In turn, protein that is not in the native state can be inactive and/or immunogenic.

In contrast to Yamasaki, applicant assessed protein stability by several methods including (1) total protein recovery by rpHPLC, (2) recovery of monomeric (non-

aggregated) protein by size exclusion chromatography (Figure 11), (3) analysis of covalently aggregated protein by SDS-Page (Figure 7), and (4) quantification of oxidized protein by peptide mapping (a measure of protein oxidation). Thus, as demonstrated by the foregoing figures, and in contrast to Yamazaki, applicant's formulations contain substantially monomeric protein as evidenced by Figures 7, 8 and 11.

While Yamazaki does teach the use of certain amino acids as stabilizers, Table 1 of this reference makes it clear that not all amino acids are useful for such purpose. In fact some amino acids, e.g. phenylalanine and cysteine, are actually destabilizing. *See also* Figure 4 of Yamazaki wherein the addition of certain amino acids leads to aggregate formation as assessed by SDS-page (evidenced by the additional bands of higher molecular weight in lanes 4 and 7). Thus, contrary to the assertion in the Office Action, Yamazaki does not teach or suggest the use of all amino acids in erythropoietin-containing compositions.

Applicant has shown that the use of methionine in the claimed compositions is the preferred antioxidant for reducing aggregate formation. There is no teaching or suggestion in Yamazaki specifically to use methionine as an antioxidant. Yamazaki is thus not a proper Section 102 reference.

Applicant submits the claims as amended are fully patentable over Yamazaki and that this rejection is overcome.

Claims 1-4, 6,7, 9-11, 22-25, 27, 28, 30-32 and 46 are also rejected under Section 102(b) and anticipated by US Patent 4,992,419 (Woog). This rejection is overcome.

Woog does not disclose applicant's aqueous erythropoietin glycoprotein product-containing compositions that are storage stable at room temperature. To make his compositions storage stable, that is provide some shelf-life, at room temperature, Woog lyophilized them. Even after reconstitution, however, the Woog formulations are only stable at room temperature for a few months. *See, e.g.*, Woog at column 4, lines 3-8. Such a short shelf-life is not commercially desirable. In contrast, Applicant's formulations are storage stable at room temperature for at least about six months. *See* Table 3, page 46, of the instant application. Thus, Woog's compositions cannot be the same as applicant's compositions.

Furthermore, Woog does not suggest the use of any anti-oxidant, and certainly not methionine.

Applicant submits the claims as amended are fully patentable over Woog and that this rejection is overcome.

Claims 1-18, 22-39,43,46,48-53,55 and 59 are rejected under Section 102(e) as being anticipated by U.S. Pat. No. 6,583,272 B1 (Bailon). This rejection is traversed.

The erythropoietin glycoprotein product-containing formulations disclosed in Bailon are the work of the inventor of the instant application. Applicant submitted in the parent application (USSN 09/853,731, CD 20619 US) a Rule 132 Declaration by inventor Dr. Papadimitriou attesting to the fact that he is the inventor of the formulations disclosed but not claimed in the Bailon patent. A copy of Dr. Papadimitriou's Declaration is again provided with this amendment. This rejection is thus traversed.

In view of the above arguments and amendments, the Section 102 rejections are overcome in part and traversed in part and should be withdrawn.

The Section 103 Rejections

Claims 1-4, 6-9, 11 and 12 are rejected under 35 USC § 103(a) as being obvious over Yamazaki, supra, in view of WO 92/06116 (Rosen et al.). This rejection is traversed.

Rosen is cited as disclosing the amino acid sequence of recombinant human EPO.

For the reasons stated above, Yamazaki does not teach or fairly suggest applicant's claimed liquid erythropoietin glycoprotein product –containing compositions that are storage stable at room temperature for at least about six months and contain methionine. Rosen's disclosure of the amino acid sequence of recombinant human EPO does not make up for the deficiencies of the primary reference, Yamazaki. Thus, even when Rosen is combined with Yamazaki, the resulting disclosure still does not teach or fairly suggest applicants' specific liquid erythropoietin glycoprotein-containing compositions that include methionine and are stable at room temperature for up to about six months without the use of serum albumin as an additive. See, e.g., the instant application at paragraphs 4, 8, and Table 3.

In addition, claims 1-4, 6-9 and 11-16 are also rejected under 35 USC § 103(a) as being obvious over Yamazaki, supra, in combination with Rosen, supra, further in view of EP 0640619 (Elliot). This rejection is also traversed.

Elliot is cited for disclosing EPO analogs having at least one additional glycosylation site.

For the reasons provided above, the combination of Yamazaki and Rosen does not teach or fairly suggest applicant's claimed liquid erythropoietin glycoprotein product –containing compositions that are storage stable at room temperature for at least about six months and contain methionine. Thus, adding a reference that merely portends to teach a modified human erythropoietin also cannot teach or suggest applicant's claimed liquid compositions.

The Section 103 rejections are also overcome and should be withdrawn.

Conclusion

In view of the above amendments and the foregoing remarks, and the copy of the concurrently submitted Rule 132 Declaration of Dr. Papadimitriou, it is respectfully submitted that the instant application is in condition for allowance and prompt allowance of the application is solicited.

Submitted with this amendment is a fee sheet for newly added claims. Should the Patent Office determine that there are owed any additional fees, or a credit is due to applicant, the Patent Office is hereby authorized to charge any required fees, including any extension of time and/or excess claim fees, or credit any overpayment, to applicant's Deposit Account 08-2525 as appropriate.

Respectfully submitted,

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Enclosures

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